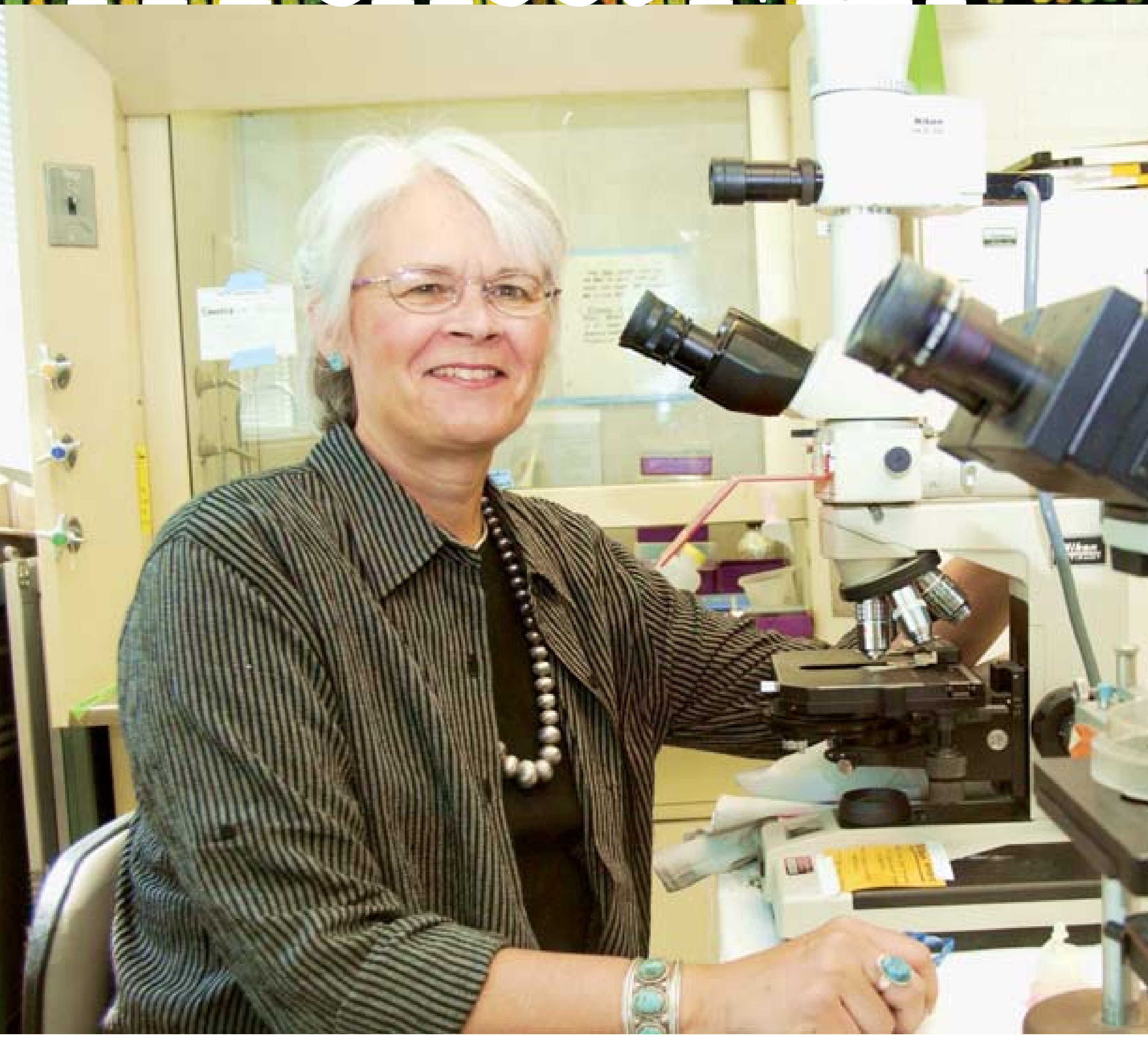
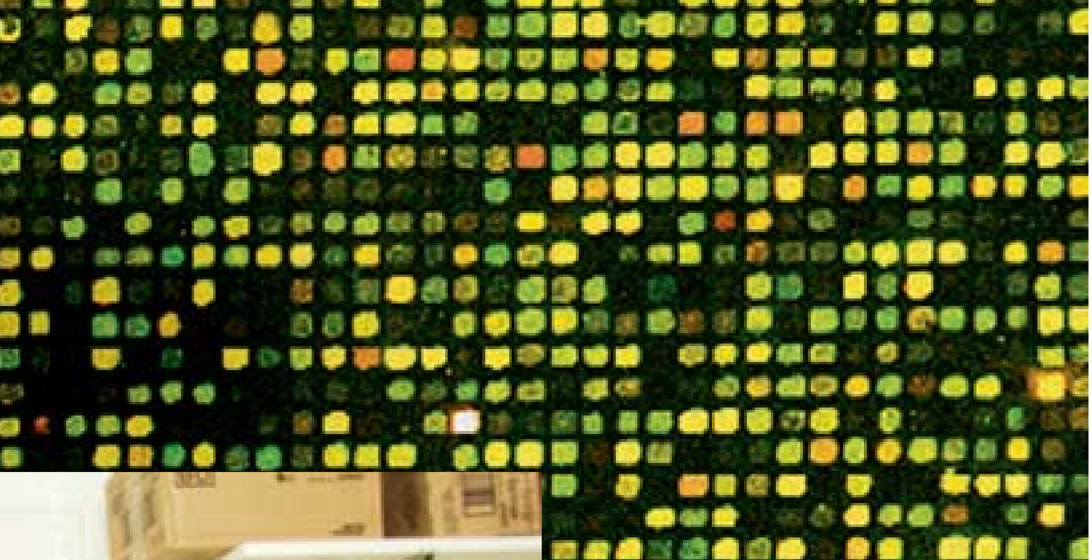
A Perfect Mix





JUANITA MARTINEZ, ANGELINA RODRIGUEZ

TOM BRAHL

"I never expected the joy of science to last so long, and I don't see it ending."

By Alison Davis

Biologist Maggie Werner-Washburne likes to mix things up.

"I have done this all my life," she says, recalling her childhood on the edge of a Mexican village within a small Iowa town. The daughter of a German father and a Mexican mother, Werner-Washburne grew up in a mixed-ethnic environment, and because of it she learned to be comfortable in two worlds.

Today, Werner-Washburne still thrives on diversity, and her lab at the University of New Mexico in Albuquerque is an ethnic blend.

Many of the graduate students who work in her lab have come from small Hispanic communities, from towns of a few hundred people, and from Native American pueblos and reservations. Werner-Washburne relishes the chance to introduce research to these students, many of whom are the first in their family or community to go to college.

"I get a lot of good students, and I try to help them make it through school without losing themselves or their culture along the way," she says. "It's not impossible."

In a similar vein, she believes that it's not impossible to bridge gaps that separate scientists working in entirely different fields. She thinks someone like herself, who has experience negotiating across cultural divides, can help accomplish this goal.

Bridging Science

In her own lab, Werner-Washburne is bridging the vastly different worlds of biology and mathematics. Her research in a field called genomics is a quest to track the activity of thousands of genes at the same time in living cells.

It's not easy to do.

Maggie Werner-Washburne is a biologist at the University of New Mexico in Albuquerque. Werner-Washburne studies quiescent cells.

To tackle this difficult research project, a potpourri of scientific personnel in Werner-Washburne's lab work together. Her coworkers include chemical engineers, computer scientists, biologists, mathematicians, chemical analysts, and statisticians. Lab members congregate in what Werner-Washburne calls a "visualization room" to exchange ideas or simply chat about the day.

It can be very hard to get interactions going in the first place, she says, because computer scientists and biologists speak two different languages.

"Biologists sometimes think computer scientists are simply programmers," says Werner-Washburne, "and mathematicians often think biologists are missing the genes for understanding math."

The key, Werner-Washburne says, is knowing enough about how another person sees the world, and what he or she does, to know what questions to ask. When you have an idea that calls on both camps to come up with their best ideas, it's like magic, she says.

Fast Track

Werner-Washburne monitors gene activity in cells at intervals considered lightning-fast compared to what has been done traditionally (every 5-10 seconds *vs.* a few minutes to several hours). She needed a new kind of tool to sample cell cultures this fast.

The trouble is, you can't just open up a scientific catalog and buy a thing to do that, she says. So her lab constructed a device called a rapid sampler that can grab small volumes of liquid, over and over again, from a culture of growing cells. Werner-Washburne, her lab technician, and an undergraduate student designed and built the contraption, working together with a chemist, a mechanical engineer, a computer scientist, and a chemical engineer.

JASON PADILLA JAETAO, ANGELINA RODRIGUEZ

A mixed group of researchers, including undergraduate student Jason Padilla Jaetao and lab technician Angelina Rodriguez, built this "rapid sampler" for about $600.

Made from scratch, the sampler cost about $600.

The device is simple: At the click of a switch, a waft of pressurized air flows into a sealed glass flask containing cells growing in a culture broth. The sudden change in pressure displaces a small amount of cell-containing liquid into a metal catch tube, which delivers the cell samples to a collecting tube. By setting the test tubes in ice water, the scientists freeze the cells' molecular activity until further processing of the samples can display their gene activity readout.

Werner-Washburne says that because biologists did not expect to need to measure rapid changes in gene activity, no one had developed a tool to do it. She is excited that her research takes her in new directions all the time.

"It's discovery-based; that's what I love about this work."

Cross-Training

Werner-Washburne's joy of discovery began years ago during a 1 1/2-year trekking expedition from Mexico through Central and South America. She had recently completed her bachelor's degree in poetry—yes, poetry—at Stanford University in California.

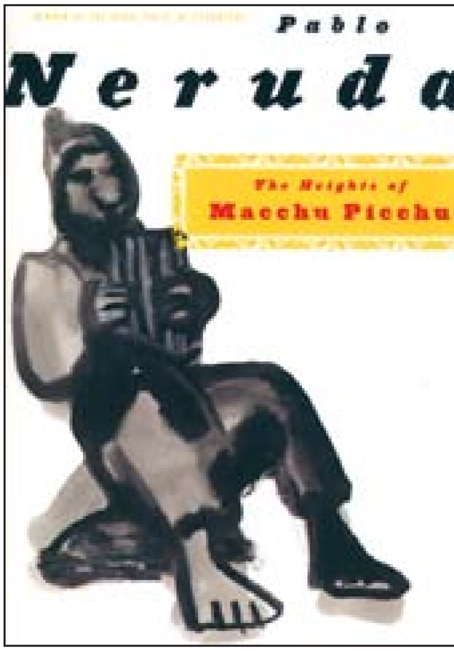
Werner-Washburne did well at Stanford, but she felt out of place and yearned to head southward to find her Latina roots. Her main goal at the time, she says, was to meet the Chilean poet Pablo Neruda, whose Nobel Prize-winning writing had electrified her.

"The minute I crossed the [Mexican] border, I knew I was home," she says.

Werner-Washburne was culturally alive and hungry for knowledge. She took everything in like a sponge. The environment, she remembers, was holistic in the sense that everyday life and science were tightly woven together. She recalls outdoor markets in Oaxaca, Mexico, where merchants sold plants for food and medicinal uses. Werner-Washburne watched locals create brilliantly colored purple cloth by harvesting the natural chemical dyes from mollusks in the nearby sea.

She continued her trek, traveling from Colombia to the Alaskan wilderness, where she worked for a year as a trapper, writer, and teacher for Outward Bound, a nonprofit educational organization. Next, Werner-Washburne worked as a paraprofessional nurse in a Minnesota health clinic serving mostly urban, single-parent Native American families. In addition to providing inspiration for ever better poetry, all of these experiences deepened her understanding of cultural diversity and nursed a growing desire to learn Western science.

Werner-Washburne took her first formal step toward becoming a scientist by signing up for courses at the University of Minnesota in St. Paul. In hopes of earning



Maggie Werner-Washburne was inspired by Pablo Neruda's epic poem, *The Heights of Macchu Picchu*. "After so much John Donne," she says, "the concept that someone could write amazing poetry about an archeological site was fascinating."

a master's degree in botany, she enrolled at the University of Hawaii in Honolulu. Her then-advisor, the late Sandy Siegel, impressed upon her the importance of being scientifically open-minded. Siegel's research interests included studying life in extreme environments, such as space and the Dead Sea.

A few years later, Werner-Washburne completed her scientific training by getting her Ph.D. and doing post-doctoral research at the University of Wisconsin in Madison. Still enamored with plant biology, she focused her attention on studying photosynthesis, the process by which plants convert carbon dioxide into energy using sunlight.

But pretty soon, there was a problem.

Although she enjoyed the topic immensely, Werner-Washburne found great difficulty answering key questions about how cells work with the molecular biology techniques available to study plants.

"There were so many things I couldn't do," she says, and she made a decision to switch to a more versatile model organism for probing basic biological questions: yeast.

Sitting Still

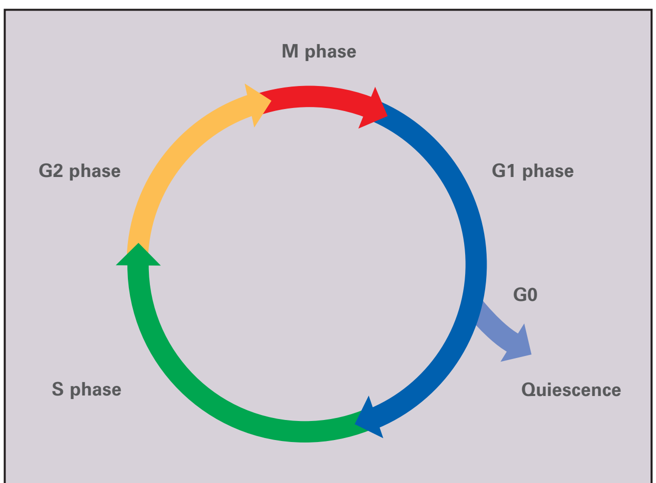
Like the cells that make up animals, plants, and people, yeast cells are eukaryotic. This means that yeast cells have compartments, such as nuclei and mitochondria. Because researchers know a lot about yeast genetics, yeast cells serve as miniature laboratories for thousands of scientists worldwide. They can easily mix and match yeast genes and figure out how the changes affect the cell.

However, the vast majority of yeast researchers focus their questions on cells that are actively growing. Werner-Washburne, on the other hand, is interested in yeast cells that do nothing but sit still. This phase of cellular life is called quiescence.

Quiescent cells are in a stalled stage of growth called stationary phase, a situation that is not unique to yeast. In fact, at any given time, almost all of the cells on the planet are "resting" in stationary phase, a stage scientists call "G-zero" (G0).

Examples of cells in G0 might include yeast cells resting on a grape leaf, the neurons in your brain, or deadly anthrax spores that lie dormant until propelled to grow by some type of signal, which is usually a source of food or energy.

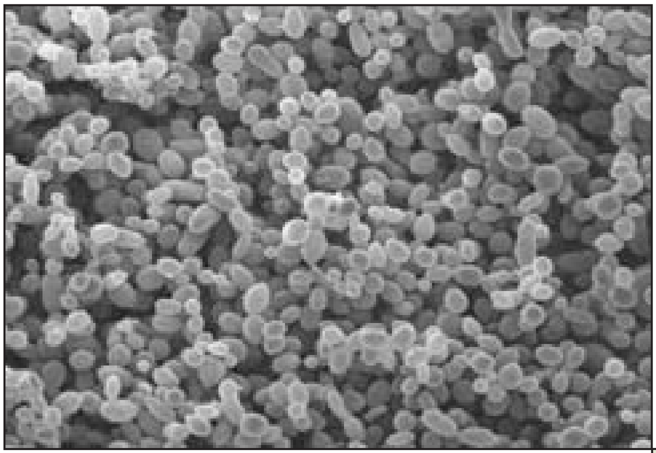
When conditions are favorable, cells that can divide progress through an orderly set of steps called the cell cycle. During the growth part of the cycle, a cell gets larger and makes copies of all its components, including its genetic material, DNA. The division part of the cycle takes place in a step called mitosis, when the cell splits and produces a mother and a daughter cell.



Cells progress through a cycle that consists of phases for growth (G1, S, and G2) and division (M). Cells become quiescent when they exit this cycle (G0).

Cells exit this cycle when they become quiescent. Something in a cell's surroundings sends a signal to stop growing. Researchers like Werner-Washburne suspect that cues in the environment set off genetic switches inside cells, tuning up or down the activity of specific genes. Deciphering the signals that push cells in and out of quiescence, and finding the genes involved, is keeping Werner-Washburne very busy.

To find quiescence signals, she looks at sequential snapshots of the millions of working parts inside a yeast cell, over thousands of points in time.



LOUIS DE VOS, FREE UNIVERSITY OF BRUSSELS

Brewer's yeast, seen here under a microscope, is a common research tool for biologists who study cells.

All Together Now

Genomics is the study of how all of an organism's genes work together. In this sort of analysis, researchers hope to eventually understand how a functioning unit—like a single organ or even the entire human body—works properly in health or improperly in disease.

Scientists who study genomics use tools called microarrays, which are glass or silicon "chips" that are imprinted with small sections of thousands of genes in a grid-like pattern. The microarrays Werner-Washburne uses for her experiments contain a unique snippet of DNA from each of the 6,000 genes in a yeast cell.

DNA's natural properties make this technology possible. Miniature molecular machines inside your cells (and those in other animals, plants, microbes, and yeast) copy DNA by making an intermediate, complementary, copy of a gene. Scientists gauge the activity of a gene by the amount of the intermediate, called messenger RNA (mRNA), that the gene makes.

Using the rapid sampler device, Werner-Washburne and her coworkers measure the activity of yeast genes by collecting data every few seconds. Inside each collecting tube, the researchers have added special enzymes that automatically make matching copies of any mRNA present. The copies, called complementary DNA (cDNA), are then applied to a gene chip. If there's an exact sequence match and a cDNA corresponds perfectly with a particular gene sequence, that gene's spot on the chip lights up, because it has been tagged with a fluorescent dye.

It doesn't take long to realize that the amount of data from this type of experiment is staggering. Thousands of genes multiplied by thousands of time points adds up to more work than one person—or even several people—can handle.

Werner-Washburne got some help from scientists at nearby Sandia National Laboratories in Albuquerque. The Sandia researchers had computer software that could process such data, and they constructed a specialized microarray scanner that could interpret and distinguish between the output of many different dye colors at once. The end result is a genomics readout (see photo, page 7).

Werner-Washburne has found that when she nudges quiescent yeast cells to wake up by adding the sugar glucose to their culture dishes, a massive change occurs in the level of almost every messenger RNA in the cell. She has identified certain genes that appear to be particularly important for the yeast cells to shift into high gear.

"When needed," she says, "these cells are set to go from 0 to 60 miles an hour in a matter of seconds or minutes."

Similarly, Werner-Washburne can study the reverse process by withdrawing food from the yeast's culture broth. By doing this, then looking for changes in gene activity, she is closing in on several yeast genes that increase their activity when it's time to slow down and enter a resting state.

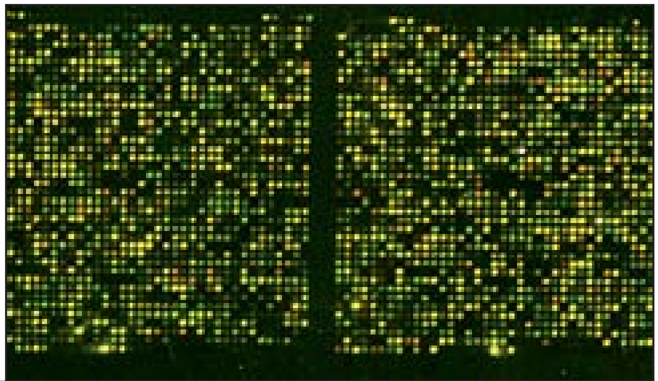
Understanding quiescence has implications for human health. Many microorganisms that cause infections, such as tuberculosis, are quiescent for weeks to months. What turns them on and off is an unsolved medical mystery.

Time for a Change

Genomic research generates an avalanche of data, and computers, statistics, and math are essential for understanding it. Werner-Washburne has learned that math-based approaches are also important for designing experiments correctly in the first place, and watching her students become increasingly comfortable with statistics and math has been gratifying.

"Biology students don't get enough math," she says. To counteract this deficiency, she holds in-lab tutorials and on-site training whenever possible. In some cases, coworkers at Sandia offer help to her students.

Thinking mathematically and crafting new tools add up to just one part of success in the exciting new research frontier of genomics. Werner-Washburne knows from personal experience that an important part of the mix is blending different cultures of people and keeping an open mind for discovery.



JUANITA MARTINEZ, ANGELINA RODRIGUEZ

Scientists use microarrays (photo) to gauge gene activity.

"I never expected the joy of science to last so long," says Werner-Washburne, "and I don't see it ending."

A Pioneering Spirit

TOM BRAHL

In Maggie Werner-Washburne's lab, graduate student Anthony Aragon has to think outside the box.

His Ph.D. thesis research project, cataloging the activity of thousands of genes in quiescent yeast cells, requires him to spend a lot more time planning his experiments than actually doing them.

"It's been really difficult for me to think this way," he says, describing paying constant attention to math and statistics in planning an experiment that will yield data he can trust. For example, Aragon says, most biologists study a process happening over time (often referred to as a time course) by performing each experimental "time point" in chronological order. But then they also process their samples and analyze their data in the same order.

"That's not really a good idea," he says. "You need to randomize each procedure to be able to identify the effect caused by time alone."

While it has been tricky for him to bend his mindset to be more mathematical, his pioneering spirit has certainly helped a lot. Aragon grew up in Manzanola, Colorado, a small, rural town of about 450 people. His close-knit Hispanic family, including grandparents, aunts, uncles, and cousins, all lived next to each other on the same street. Aragon was the first in his family to graduate from high school and the first in his town to go to graduate school.

While Aragon says it was a big deal for him to leave home for his education, he says his family has been very supportive. He also feels at home in Werner-Washburne's lab where he finds the research exciting and the atmosphere nurturing.

"Maggie is always ready to talk," he says.—*A.D.*